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(71) Applicant *(for all designated States except US)*: A + SCIENCE INVEST AB [SE/SE]; Kungsportavenyn 31–35, S–400 10 Göteborg (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: PETTERSSON, Anders [SE/SE]; Knaverstad 130 66, S–442 97 Kode (SE). FÄNDRIKS, Lars [SE/SE]; Askims Ängsväg 14, S–436 40 Askim (SE).

(74) Agent: AWAPATENT AB; P.O. Box 11394, S–404 28 Göteborg (SE).

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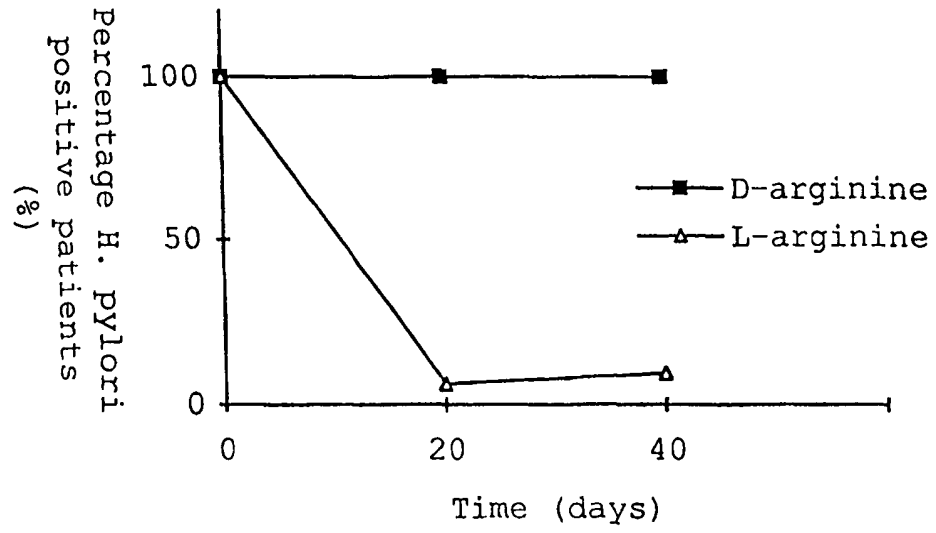
(54) Title: USE OF L–ARGININE OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF FOR PRODUCTION OF DRUGS FOR TREATMENT OF *HELICOBACTER PYLORI* INFECTIONS



(57) Abstract

The present invention relates to the use of L–arginine, at least one of its pharmaceutically acceptable salts or a mixture thereof for production of a drug intended for oral, parenteral, or rectal administration for treatment of infections caused by *Helicobacter pylori*. The active substance may be included in the drug in its neutral form or as a pro–drug, which is later metabolised by a host into the active form. Furthermore, the drug may include an inert vehicle and/or other pharmaceutically acceptable additives.

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USE OF L-ARGININE OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF FOR PRODUCTION OF DRUGS FOR TREATMENT OF HELICOBACTER PYLORI INFECTIONS

Field of the invention

The present invention relates to the use of L-arginine or a pharmaceutically acceptable salt thereof for production of a drug for treatment of infections caused by *Helicobacter pylori*.

Background of the invention

Helicobacter pylori is a gram-negative, microaerophilic, curved bacteria, which causes infections in the stomach in humans and some other species, such as pig, monkey, and horse. Approximately 30% of the population in the western countries is affected by *Helicobacter pylori* infections. *Helicobacter pylori* causes a local inflammation, called antrum gastrit, and contributes to other pathological conditions in the gastrodudenal tract. This is mainly related to gastric ulcer, but the infection is also considered as an important factor in the development of atrophic gastritis, stomach cancer and stomach lymphoma. Eradication of the bacteria also cures the ulcer disease.

Medication used for treatment of *Helicobacter pylori* infections normally consists of antibiotics in combination with bismuth salts and/or antacids, such as histamine-2 receptor antagonists or proton pump inhibitors. The effect of this medication is limited due to the fact that it involves a combination of several drugs, resulting in an increase of the side-effects, which leads to a decreased patient compliance, i.e. the patient does not use the drugs in the prescribed way, and high drug costs.

Another alternative for treatment of *Helicobacter pylori* infections is the use of vaccination, either per oral vaccination or parental administered vaccination. Vaccination leads to an activation or a stimulation of

the host's immunological defence. However, since *Helicobacter pylori* infections are chronic infections, the bacteria may develop a certain resistance against this immunological defence, and it is thus difficult to develop an effective vaccine against *Helicobacter pylori*.

From EP-A-0 689 835 it is known to use a nutrient composition comprising a mixture of 17 different amino acids, including L-arginine, and a fatty acid for the treatment of inflammatory bowel disease. However, since this nutrient composition includes 17 different amino acids, it is relatively complicated to produce.

From JP-A-07267855 it is known to use a glutamine-producing agent containing several amino acids, including L-arginine, e.g. to obtain an antiulcerative effect. According to this document it is thus also necessary to use a combination of different amino acids in order to obtain the desired effect.

Summary of the invention

It has now surprisingly been found that a drug containing L-arginine, preferably in the form of a tablet, is effective for eradication of *Helicobacter pylori* in mammals and other species. Thus, the present invention relates to the use of L-arginine or a pharmaceutically acceptable salt thereof for production of a drug for treatment of infections caused by *Helicobacter pylori*.

The characterising features of the invention will be evident from the following description and the appended claims.

Brief description of the drawing

The invention will now be described in further detail hereinafter with reference to the accompanying drawing on which:

Fig. 1. shows a graph illustrating the percentage of patients positive for *Helicobacter pylori* after treatment with L-arginine and D-arginine, respectively.

Detailed description of the invention

Thus, the present invention relates to the use of L-arginine, at least one of its pharmaceutically acceptable salts or a mixture thereof for production of a drug or a pharmaceutical composition for treatment of infections caused by *Helicobacter pylori*.

The drug may be intended for oral administration, parenteral administration, or rectal administration. The drug may also be intended for delayed release of the active substance.

The active substance may be included in the drug in its neutral form, as a salt or as a pro-drug, which is metabolised by the intended recipient into the active form.

Furthermore, the drug may include an inert vehicle and/or other pharmaceutically acceptable additives.

The drug according to the invention is suitable for use in combination with other substances affecting *Helicobacter pylori* infections, such as antibiotics, histamine-2 receptor antagonists, bismuth salts, proton pump inhibitors, ascorbic acid, antacids or sucralfate.

An appropriate dosage is 0.01-30 g L-arginine divided into 1-5 administrations.

The invention will now be further explained in the following example. This example is only intended to illustrate the invention and should in no way be considered to limit the scope of the invention.

Example

Helicobacter pylori bacteria were detected by the so called urea breath test, UBT. This test, which is well known to persons skilled in the art, is based on the fact

that *Helicobacter pylori* bacteria in the stomach metabolise urea into carbon dioxide and water. The carbon dioxide will then be emitted in the breath. If a patient infected with *Helicobacter pylori* bacteria drinks a liquid containing isotope labelled urea his breath will then contain isotope labelled carbon dioxide.

20 patients tested positive for *Helicobacter pylori* bacteria with the above mentioned test were used in this example. 10 of these patients were treated with tablets containing L-arginine during 14 days. The dosage used was 1 g given 3 times daily. The remaining 10 patients, constituting a control group, were treated in the same way but with tablets containing D-arginine instead of L-arginine.

The presence of *Helicobacter pylori* bacteria was controlled with the urea breath test 20 and 40 days after day one, i.e. when the first tablet was administered. The result of these tests is shown in figure 1.

It is clearly evident that the treatment with L-arginine was successful in eradication of *Helicobacter pylori* bacteria.

CLAIMS

1. Use of L-arginine or a pharmaceutically acceptable salt thereof for production of a drug for treatment of *Helicobacter pylori* infections.

2. Use of L-arginine according to claim 1, characterised in that the drug is intended for oral administration.

3. Use of L-arginine according to claim 1, characterised in that the drug is intended for parenteral administration.

4. Use of L-arginine according to claim 1, characterised in that the drug is intended for rectal administration.

5. Use of L-arginine according to any one of claims 1-4, characterised in that the active substance is included in the drug in its neutral form.

6. Use of L-arginine according to any one of claims 1-4, characterised in that the active substance is included in the drug as a pro-drug, which may be metabolised by a host into the active form.

7. Use of L-arginine according to any one of claims 1-6, characterised in that the drug comprises an inert vehicle.

8. Use of L-arginine according to any one of claims 1-7, characterised in that the drug is suitable for use in combination with other substances affecting *Helicobacter pylori* infections, such as antibiotics, histamine-2 receptor antagonists, bismuth salts, proton pump inhibitors, ascorbic acid, antacids or sucralfate.

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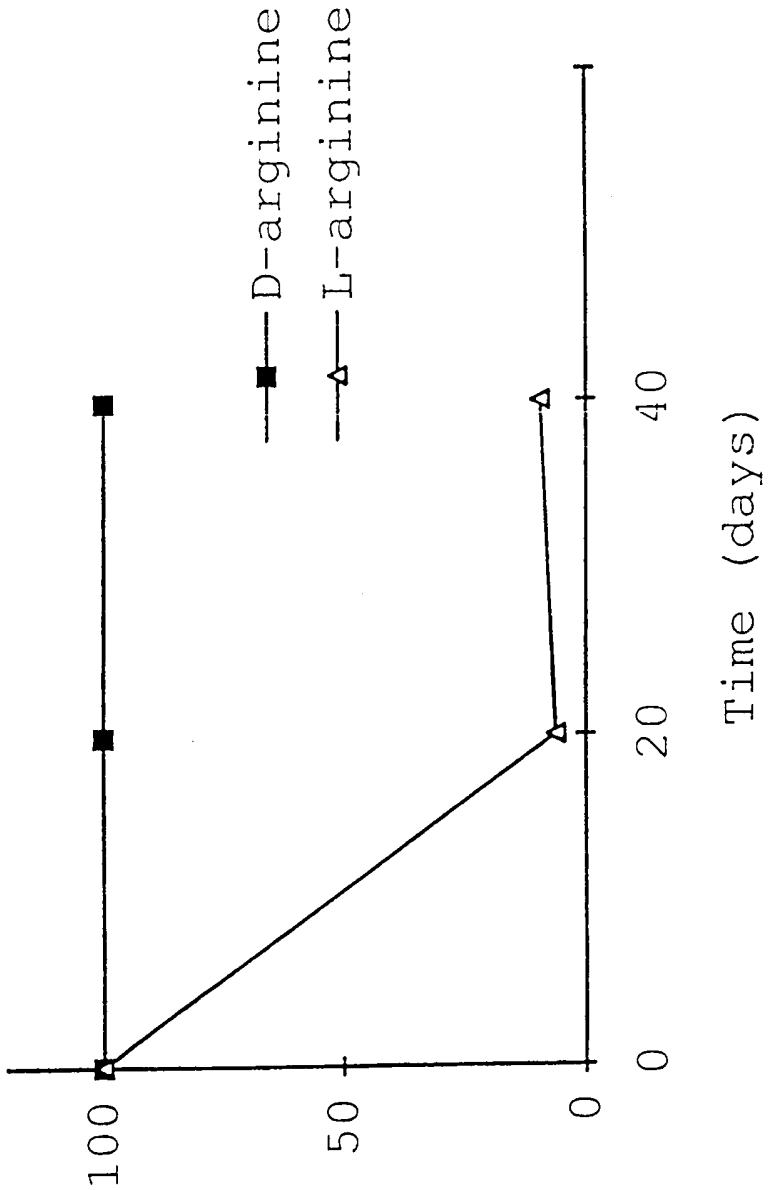
D-arginine
L-arginine
Time (days)
0
20
40
100
50
0
Percentage H. pylori positive patients (%)

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01101

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/195
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA,WPI,IFIPAT,EMBASE,MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0689835 A2 (AJINOMOTO CO.,INC.), 3 January 1996 (03.01.96) --	1-8
A	JP 7-267855 A (TAIHO YAKUHIN KOGYO KK OTSUKA PHARMACEUT FACTORY INC.), 17 October 1995 (17.10.95) --	1-8
A	Applied and Environmental Microbiol, Volume 60, No 9, 1994, P.Nedenskov, "Nutritional Requirements for Growth of Helicobacter pylori" page 3450 - page 3453 --	1-8

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
21 January 1998	27 -01- 1998
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PCT/SE 97/01101

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Cancer Lett., Volume 102, 1996, K.B. Shapiro et el, "Induction of Nitric Oxide Synthesis in Murine Macrophages by Helicobacter pylori" page 49 - page 56 -- --------	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

07/01/98

International application No. PCT/SE 97/01101

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0689835 A2	03/01/96	JP 8073351 A	19/03/96
JP 7-267855 A	17/10/95	NONE	